REMARKS

Claims 1-5, 7-20, 25-26, and 30-32 were pending, and were rejected by the Examiner. Applicants have amended claims 1, 12, and 25 to recite that there exists an amount of the fusion toxin that (a) does not result in life-threatening hepatic toxicity when administered subcutaneously; and (b) results in a decrease in the size of a tumor when administered into the tumor. Support for this amendment can be found in Applicants' specification. For example, the section of Applicants' specification extending from page 20, line 12 to page 21, line 6 discloses that subcutaneous administration of the DTAT fusion toxin to mice at a dose of 20 μg every other day for five doses had only minor, non-life-threatening effects on the liver. In addition, Applicants' specification at page 19, lines 19-30 discloses that intratumoral injection of DTAT at the same dosage resulted a decrease in tumor size.

Claim 26 also has been amended to recite an article of manufacture containing packaging material and the pharmaceutical composition of claim 25. Support for this amendment can be found in Applicants' specification at, for example, page 14, lines 2-3. No new matter has been added by either of the above amendments.

In light of these amendments and the following remarks, Applicants respectfully request allowance of claims 1-5, 7-20, 25-26, and 30-32.

Interview summary

Applicants' representatives thank the Examiner for the courtesy of a telephonic interview on June 29, 2004, and for her helpfulness during the course of the interview. Potential claim amendments and the outstanding rejection under 35 U.S.C. § 103(a) were discussed during the interview.

Rejection under 35 U.S.C. § 112

The Examiner rejected claim 26 under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner stated that it is unclear how the limitation "[a]n article of manufacture" would further limit the pharmaceutical composition of claim 25.

While Applicants respectfully submit that claim 26 implicitly further limits claim 25, Applicants have amended claim 26 to expedite prosecution of the instant application. Amended claim 26 recites that the article of manufacture comprises packaging material as well as the pharmaceutical composition of claim 25. Thus, amended claim 26 is clearly limited with respect to claim 25.

In light of the above, Applicants respectfully request withdrawal of the rejection of claim 26 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1-5, 7-20, 25-26, and 30-32 under 35 U.S.C. § 103(a) as being unpatentable over Rajagopal *et al.* (*J. Biol. Chem.* 2000, 275:7566-7573) or Oldfield *et al.* (*Curr. Topics Microbiol. Immunol.* 1998, 234:97-114), both in view of Greenfield *et al.* (*Science* 1987, 238:536-539) and Fabbrini *et al.* (*FASEB J.* 1997, 11:1169-1176), and Mori *et al.* (*J. Neurooncol.* 2000, 46:115-123). The Examiner also rejected claims 13 and 15 under 35 U.S.C. § 103(a) as being unpatentable over the above references in further view of the Leppala *et al.*, Wels *et al.*, Arnon, McDonald *et al.*, Morishita *et al.*, Pastan *et al.*, Baty *et al.*, el Kouhen *et al.*, Geoff *et al.*, Bouveret *et al.*, Lacy *et al.*, Wiedlocha *et al.*, and Olsnes *et al.* references, which read on particular toxins and toxin domains. The Examiner stated that given the teachings of the cited references, it would have been *prima facie* obvious for a person having ordinary skill in the art at the time the claimed invention was made to make and use the fusion toxins as recited in the present claims.

Applicants respectfully disagree. In particular, Applicants submit that there would have been no motivation for a person having ordinary skill in the art to combine the disclosures of the cited references and hence to practice the instant invention. Moreover, Applicants submit that any motivation a person of ordinary skill in the art might have had would have constituted no more than an invitation to try, without the least expectation of success. Despite these considerations, however, Applicants have amended claims 1, 12, and 25 based on the Examiner's suggestion during the telephonic interview of June 29, 2004. Thus, the claims now recite that there exists an amount of the fusion toxin that does not result in life-threatening hepatic toxicity when administered subcutaneously, and results in a decrease in the size of a tumor when

administered into the tumor. As discussed below, the presently claimed methods are patentable over the cited art.

The Rajagopal *et al.* reference discloses that since the urokinase-type plasminogen activator (uPA) receptor (uPAR) is expressed on human liver, systemic administration of fusion toxins containing the amino terminal fragment (ATF) of uPA may well be toxic. In addition, the Oldfield *et al.* reference discloses that toxicity of immunotoxins can occur when the target is expressed on normal, nonmalignant cells. In this regard, the Mori *et al.* reference cited by the Examiner, as well as other references that Applicants could provide if the Examiner so wishes, have shown that (a) uPAR is expressed by vascular endothelial cells, including brain vascular endothelial cells; (b) expression of uPAR on such cells is greatly increased by vascular endothelial growth factor (VEGF); and (c) brain cancer cells produce and stimulate the production of VEGF. Thus, a person of ordinary skill in the art would not only have been dissuaded by the cited art from administering uPA-containing immunotoxins to subjects, such a person also would not have been motivated to administer a uPA-containing immunotoxin directly into the brain of a subject with a brain tumor.

The Greenfield *et al.*, Fabbrini *et al.*, and Mori *et al.* references fail to contradict the teachings of the Rajagopal *et al.* and Oldfield *et al.* references. Moreover, none of the other cited references provide any suggestion contrary to the teachings of the Rajagopal *et al.* and Oldfield *et al.* references that systemic administration of a fusion toxin as recited in claims 13 and 15 would not be toxic to areas outside a tumor. Thus, the combination of cited references and the knowledge in the art at the time the present application was filed fail to provide the requisite suggestion or motivation to combine the teachings disclosed in the cited references and hence practice the presently claimed methods.

Applicants further submit that the lack of hepatic (and other) toxicity after subcutaneous administration of the immunotoxin in an amount that was therapeutic when administered intratumorally (see Applicants' specification at page 19, line 19 to page 21, line 6) constitutes a surprising result in view of the above-described teachings of the cited art and the knowledge in the art at the time the application was filed. In fact, the potentially toxic effects of fusion toxins such as DTAT are acknowledged in Applicants' specification. In particular, the text at page 20,

lines 19-21 of the specification stresses the importance of Applicants' evidence that DTAT was not toxic when administered systemically.

In response to the Examiner's comments on pages 8 and 9 of the outstanding Office Action, Applicants note that: (1) the DT portion of the DTAT fusion toxin contains three LVD-related motifs (see, e.g., Table 1 of the Baluna *et al.* reference); (2) prophylactic administration of cholorquine as disclosed by the Hagihara *et al.* reference is not required by the present claims, nor was chloroquine administration ever contemplated in the instant application; and (3) uPAR is present on vascular cells, as discussed above, and thus DTAT might be expected to target cells outside of tumor areas. As such, the success of the presently claimed methods is surprising and could not have been predicted based on the teachings of the Rajagopal *et al.*, Fabbrini *et al.*, Greenfield *et al.*, Oldfield *et al.*, and Mori *et al.* references, either alone or in combination.

In summary, Applicants submit that neither the cited references nor the knowledge of those skilled in the art at the time the present application was filed would have provided the requisite motivation to combine the disclosures of the cited references and hence to practice the invention embodied in the instant claims. Moreover, any putative motivation that might have existed would have constituted at best an invitation to try, without the least expectation of success. More importantly, the findings of the toxicity and therapy studies described in Example 3 of the instant application constitute a surprising and unexpected result, which is now incorporated into the present claims.

In light of these remarks and the amendments presented herein, Applicants respectfully request withdrawal of the rejection of claims 1-5, 7-20, 25-26, and 30-32 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully submit that present claims 1-5, 7-20, 25-26, and 30-32 are in condition for allowance, which action is requested. The Examiner is invited to telephone the undersigned if such would further prosecution.

Applicants believe that no fee is due. Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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